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TITLE: Blood Biomarker Profile of TBI-Associated Cognitive Impairment Among Old and Young Veterans

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14. ABSTRACT The goal of this project is to define the biomarker profile of TBI-associated cognitive impairment (CI) in veterans and compare it to that of veterans with Alzheimer's Disease (AD) and to age-matched controls. Our overall hypothesis is that TBI-associated CI involves a unique biomarker profile that has features distinguishable from AD and normal aging. Specifically, we hypothesize that: 1) patients with TBI associated CI will have higher phospho-tau/total tau ratio than controls who have not had a TBI, and that 2) TBI-associated CI will be associated with elevations in inflammatory markers compared to controls and 3) a decrease in b-amyloid measures compared to controls but not as low as in the setting of AD. We recently completed enrollment. Data from 160 participants has been collected (66 TBI, 54 controls, and 40 with AD and no TBI). Now that data collection is complete, we will examine the biomarker profile of the groups. This study will refine our understanding of the underlying mechanisms in TBI-associated CI, help predict who is at greatest risk of developing CI in veterans with TBI, and identify who may benefit from interventions and treatment for CI and its prevention.					
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Introduction

Military personnel are at high risk for traumatic brain injury (TBI). Two well-recognized and important adverse outcomes of TBI are cognitive impairment (CI) and dementia. While most studies report a 2-3 times increased risk of dementia associated with TBI, the underlying mechanism and type of dementia associated with TBI remains unclear. Some studies link TBI to Alzheimer disease (AD) while others suggest the TBI-associated dementia is more similar to chronic traumatic encephalopathy (CTE). The goal of this project is to define the biomarker profile of TBI-associated CI in veterans and compare it to that of veterans with AD and to age-matched controls. Our overall hypothesis is that TBI-associated CI involves a unique biomarker profile that has features distinguishable from AD and normal aging. Specifically, we hypothesize that: 1) patients with TBI associated CI will have higher phospho-tau/total tau ratio than controls who have not had a TBI, and that 2) TBI-associated CI will be associated with elevations in inflammatory markers compared to controls and 3) a decrease in b-amyloid measures compared to controls but not as low as in the setting of AD. This study will refine our understanding of the underlying mechanisms in TBI-associated CI, help predict who is at greatest risk of developing CI in veterans with TBI, and identify who may benefit from interventions and treatment for CI and its prevention.

Key Words

Traumatic brain injury (TBI), dementia, chronic traumatic encephalopathy (CTE), blood biomarkers, aging, cognitive impairment (CI), Alzheimer's disease (AD)

Accomplishments

- **What were the major goals of the project?**
 - Planning, study design, and regulatory approval
 - Study protocols were approved at both sites in the first quarter of the project. The study protocol, measurements and operations manual were completed in the first six months as planned.
 - Identify and enroll older veterans with TBI and normal controls at Armed Forces Retirement Home (AFRH), Washington, DC, and Veterans Home of California-Yountville (VHC-Y), Yountville, CA
 - Data collection is complete. We have data from 66 veterans with TBI and 54 normal controls.
 - Enroll veterans with mild Alzheimer Disease (AD) at AFRH and VHC-Y
 - Data collection is complete. We have data from 40 veterans with mild AD.
 - Identify blood biomarker profile of TBI and compare to that of AD and controls
 - Nothing to report

- **What was accomplished under these goals?**

For the entire past year, our focus has been on recruiting and expanding our AD group, and we nearly doubled the size of that group. We have now finished enrollment. Enrollment was challenging because the AFRH site stopped recruiting in the middle of the study due to difficulties with onsite research approvals. We extended recruitment at the VHC-Y site to compensate and met nearly 70% of our recruitment goal, which will be sufficient for analysis. All the samples at both sites are frozen and ready to ship out for the biomarker analysis. For the analysis, we are collaborating with Quanterix and Jessica Gill at NIH. We expect to get the specimens shipped in the next few weeks, and will begin the blood biomarker analysis by the end of the year.

As of 30-SEP-2017, the end of our enrollment period, data has been collected on a total of 160 participants at both study sites: 54 cognitively normal veterans with no TBI history (controls), 66 veterans with a history of TBI, and 40 veterans with AD and no past head injuries. The breakdown of participants by site is as follows:

AFRH: Total = 47

Controls: 18

TBI: 18

AD: 11

Yountville: Total = 113

Controls: 36

TBI: 48

AD: 29

Total = 160

Controls: 54

TBI: 66

AD: 40

In the past year we had regular conference calls and e-mail contact with the sub-site USUHS/AFRH regarding study progress and future plans and will continue this close working relationship throughout the analysis and end of the project.

- **What opportunities for training and professional development has the project provided?**
 - Nothing to report
- **How were the results disseminated to communities of interest?**
 - Nothing to report
- **What do you plan to do during the next reporting period to accomplish the goals?**
 - In the final reporting period we will work closely with Dr. Gill's lab and Quanterix on measuring the biomarker assays. We anticipate data from Dr. Gill's lab in the spring. Once we have the biomarker results from the samples, we will begin to analyze and interpret the results, comparing the biomarker profiles of veterans with TBI, controls, and veterans with mild AD, and write them up for publication.

Impact

- **What was the impact on the development of the principal discipline(s) of the project?**
 - Nothing to report
- **What was the impact on other disciplines?**
 - Nothing to report
- **What was the impact on technology transfer?**
 - Nothing to report
- **What was the impact on society beyond science and technology?**
 - Nothing to report

Changes/Problems

- **Changes in approach and reasons for change**
 - Nothing to report
- **Actual or anticipated problems or delays and actions or plans to resolve them**
 - As reported in our quarterly reports, and our last annual report, the AFRH site experienced delays and difficulties in receiving permission to continue to perform research at AFRH. They were unable to resolve these issues and thus, additional recruitment was done at the VHC-Y site. Due to the delay, we requested and received a 1 year Extension Without Funds (EWOFF).
- **Changes that had a significant impact on expenditures**
 - Due to the delay at AFRH, we requested and received an EWOFF to complete the project as originally designed.
- **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**
 - Nothing to report

Products

- **Publications, conference papers, and presentations**
 - **Journal publications.**

Related Publications:

1. Gardner RC, Peltz CB, Kenney K, Covinsky KE, Diaz-Arrastia R, Yaffe K. Remote traumatic brain injury is associated with motor dysfunction in older military veterans. *J Gerontol Ser A-Biol Sci Med Sci.* 2017; 72(9):1233-1238.
2. Peltz CB, Gardner RC, Kenney K, Diaz-Arrastia R, Kramer JH, Yaffe K. Neurobehavioral Characteristics of Older Veterans with Remote Traumatic Brain Injury. *J Head Trauma Rehabil.* 2017; 32(1): E8-E15.

3. Kaup AR, Peltz C, Kenney K, Kramer JH, Diaz-Arrastia R, Yaffe K. Neuropsychological Profile of Lifetime Traumatic Brain Injury in Older Veterans. Journal of the International Neuropsychological Society. 2017; 23(1):56-64.
4. Kaup AR, Yaffe K. Reassuring News About Football and Cognitive Decline?: Not So Fast. JAMA Neurology. 2017 Jul 3. [Epub ahead of print]
 - **Books or other non-periodical, one-time publications.** Nothing to report
 - **Other publications, conference papers, and presentations.** Nothing to report
- **Website(s) or other Internet site(s)**
Nothing to report
- **Technologies or techniques**
Nothing to report
- **Inventions, patent applications, and/or licenses**
Nothing to report
- **Other Products**
Nothing to report

Participants and other collaborating organizations

- **What individuals have worked on the project?**

Name:	<i>Kristine Yaffe</i>
Project Role:	<i>Principal Investigator</i>
Researcher Identifier (e.g. ORCID ID):	<i>KYAFFE</i>
Nearest person month worked:	<i>1</i>
Contribution to Project:	<i>Dr. Yaffe provides leadership and oversees research and data collection at both sites.</i>
Funding Support:	<i>n/a</i>

Name:	<i>Kimbra Kenney</i>
Project Role:	<i>Co-Investigator</i>
Researcher Identifier (e.g. ORCID ID):	<i>KKENNEY</i>
Nearest person month worked:	<i>1</i>
Contribution to Project:	<i>Dr. Kenney provides neurological expertise and oversees the data collection and neurological battery at the AFRH site.</i>
Funding Support:	<i>n/a</i>

Name:	<i>Joel Kramer</i>
Project Role:	<i>Co-Investigator</i>
Researcher Identifier (e.g. ORCID ID):	<i>JKRAMER</i>
Nearest person month worked:	<i>1</i>
Contribution to Project:	<i>Dr. Kramer provides cognitive testing expertise and oversees the neuropsychological testing.</i>
Funding Support:	<i>n/a</i>

Name:	<i>Carrie Peltz</i>
Project Role:	<i>Project Coordinator</i>
Researcher Identifier (e.g. ORCID ID):	<i>n/a</i>
Nearest person month worked:	<i>2</i>
Contribution to Project:	<i>Dr. Peltz coordinates the project at both sites and monitors the day-to-day progress at the VHC-Y site.</i>
Funding Support:	<i>n/a</i>

Name:	<i>Kim Kelley</i>
Project Role:	<i>Research Assistant</i>
Researcher Identifier (e.g. ORCID ID):	<i>n/a</i>
Nearest person month worked:	<i>6</i>
Contribution to Project:	<i>Ms. Kelley collects data at the VHC-Y site.</i>
Funding Support:	<i>n/a</i>

Name:	<i>Dan Freimer</i>
Project Role:	<i>Research Associate</i>
Researcher Identifier (e.g. ORCID ID):	<i>n/a</i>
Nearest person month worked:	<i>1</i>
Contribution to Project:	<i>Mr. Freimer assists with project coordination and data collection at the VHC-Y site.</i>
Funding Support:	<i>n/a</i>

Name:	<i>Cora Davis</i>
Project Role:	<i>Research Assistant</i>
Researcher Identifier (e.g. ORCID ID):	<i>n/a</i>
Nearest person month worked:	<i>3</i>
Contribution to Project:	<i>Ms. Davis collects data at the AFRH site.</i>
Funding Support:	<i>n/a</i>

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

Dr. Yaffe:

Summary: Dr. Yaffe had one grant begin in the past year.

Title: Healthy Heart, Healthy Brain? A Pooled Life-course Cohort for Dementia Risk Assessment (Yaffe: Multiple PI)

Time Commitment: 1.35 calendar months

Supporting Agency: NIH: NIA

Performance Period: 05/2017-04/2021

Level of Funding: \$1,384,845

Dr. Kenney:

Summary: Dr. Kenney had no changes in the past year.

Dr. Kramer:

Summary: Dr. Kramer had one grant begin.

Title: Novel imaging and endothelial biomarkers of small vessel cerebrovascular disease (Kramer: PI)

Time Commitment: 1.8 calendar month

Supporting Agency: NIH: NINDS

Performance Period: 09/2016-07/2018

Level of Funding: \$951,149 DC

- **What other organizations were involved as partners?**
 - Nothing to report

Special Reporting Requirements

Nothing to report